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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/134,333	08/14/1998	SHIRLEY LONGACRE-ANDRE	0660-0135-0X	7863

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/134,333	LONGACRE-ANDRE ET AL.	
	Examiner	Art Unit	
	James L Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2002 and 18 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *134-137,139-143,145 and 148-175* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *134-137,139-143,145 and 148-175* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The amendments filed 20 September 2002 and 18 July 2003 are acknowledged and have been entered. Claims 150-175 are newly added. Claims 68-133, 138, 144, 146, and 147 have been cancelled. Claims 134-137, 139-143, 145, and 148-175 remain in the case.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application clearly fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for at least the following reason(s): the entry of "SEQ ID NO:" identifiers for every appearance of sequences in the description or claims of the patent application has not been directed as required.

Applicant is required to direct the entry of "SEQ ID NO:" identifiers for every appearance of sequences in the description or claims of the patent application. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g).

The disclosure is objected to because of the following informalities: the "Brief Description of the Drawings" does not contain a description of Figs. 12A through 12F as depicted on sheets 36/59 through 41/59 of the drawing sheets; the "Brief Description of the Drawings" does not contain a description of Figs.

13A-13F, 14A-14B, or 15 as depicted on sheets 51/59 through 59/59 of the drawing sheets. Appropriate correction is required.

Applicant is now required to submit drawings acceptable for printing within the time period set in the Office action. See 37 CFR 1.85(a). Submission of corrected drawings may no longer be held in abeyance pending the indication of allowable subject matter. Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

The specification is objected to and claims 134-137, 139-143, 145, and 148-175 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons similar to those of record set forth with regard to the prior similar subject matter of claims 68-149, that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 20 September 2002 have been fully considered but they are not deemed to be persuasive.

Applicant urges that the level of skill is high in this field of biotechnology and that the disclosures of Figs. 1A-1D, 2, and 4 illustrate various recombinant sequences useable in the invention. This is not found persuasive for the reasons

of record: that the skilled artisan cannot envision the detailed chemical structures of the full scope of recombinant proteins encompassed by the rejected claims because one cannot conceive that which is not disclosed and which is only described by a statement that it is part of the invention and a reference to a potential method for isolating it; that a generic statement which defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus; and, that an enabling disclosure for the preparation and use of a single analog, or only a few analogs, of a product does not enable all possible analogs where, as here, the characteristics of the analogs are unpredictable. In this regard, the disclosures of several sequences of MSP-1 protein from *Plasmodium vivax*, which are excluded from the claimed invention, several sequences from *P. falciparum* strains, and a single sequence of the p19 fragment of the MSP-1 protein of a single isolate of *P. cynomolgi*, which have portions identical to portions of MSP-1 protein from *P. vivax* which are excluded from the claimed invention, are not seen to support the full scope of the invention which also includes unknown unpredictable sequences from other isolates or from other species of malarial parasites such as from *P. malariae* or from *P. ovale*. Moreover, the arguments are not found persuasive for the further reasons of record: that the portions or epitopes are ill-defined as the amino acids required are not disclosed; that the source and reactivity of the antisera are not defined in such a manner that one, absent further description and guidance from applicant, would be apprised of which antisera or epitopes with unknown structures and/or properties are predictably encompassed and functional and/or

required in the invention; that the specification merely shows that the intact p19 fragment may inhibit parasitemia, thus, the skilled artisan would require further undue experimentation to define those structurally unpredictable portions or epitopes sufficient to inhibit parasitemia in vivo in a host; and, that an enabling disclosure for the preparation and use of a single analog, or only a few analogs, of a product does not enable all possible analogs where, as here, the characteristics of the analogs are unpredictable. Applicant's arguments do not address the lack of description and guidance to recombinant portions or particular epitopes which function in the invention.

Claims 134-137, 139-143, 145, 148-175 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 134-137, 139-143, 148, and 150, the recitation of "human antisera" is entirely vague and indefinite because sufficient definition of source and reactivity of the antisera are lacking for one to know what antisera and epitopes are encompassed.

In claim 137, it is not clear what in claim 134 is being further limited as the claim appears to limit the intended use of the composition rather than any component of the composition.

Claims 139-142 are vague and indefinite because it is unclear what is encompassed by "p33" or what "region" thereof is intended by applicant as

encompassed. It is not clear if the C-terminal region is part of the "essential constituent polypeptide" sequence.

In claims 143 and 150, it is not clear how a cell is infected with the protein or how infection of a cell with MSP-1 protein relates to a recombinant protein comprising a fragment of the protein as the "essential constituent polypeptide" sequence. In these claims, "the" membrane and "the" MSP-1 protein lack antecedent basis.

In claim 148, it is not clear which, or if all, components of the composition are conjugated.

In claims 145 and 149, the recitation of "human antisera" is entirely vague and indefinite because sufficient definition of source and reactivity of the antisera are lacking for one to know what antisera and epitopes are encompassed.

In claims 151-153 and claims dependent thereupon, it is not clear what sequences are encompassed in the absence of the recitation of "SEQ ID NO:" identifiers.

In claim 152 and claims dependent thereupon, it is unclear what missing components (a) or (b) are encompassed.

In claim 153 and claims dependent thereupon, it is unclear what missing components (a) through (d) are encompassed.

In claim 154, it is believed that --(p19)-- was intended.

Claims 157-159 and claims dependent thereupon are vague and indefinite because it is unclear what is encompassed by "p33" or what "region" thereof is

intended by applicant as encompassed. It is not clear if the C-terminal region is part of the "essential constituent polypeptide" sequence.

In claims 160-162, "the" cleavage and "the" same MSP-1 protein lack antecedent basis.

In claim 166, "the" membrane and "the" MSP-1 protein lack antecedent basis. In this claim it is not clear how a recombinant protein comprising a fragment of the MSP-1 protein as the "essential constituent polypeptide" sequence relates to MSP-1 expressed in a cell.

In claim 74, it is believed that --carrier-- was intended.

Applicant's arguments filed 20 September 2002 have been fully considered but they are not deemed to be persuasive. Applicant urges that "antisera" is a known term and is therefore not indefinite. This is not found persuasive for the reasons of record that one would not know what antisera and epitopes are encompassed absent some definition of source and reactivity of the antisera. Applicant urges, with regard to claim 137, that a long term response is in contrast to a short or intermediate term response. This is not found persuasive for the reasons of record that it is unclear what component in the composition, if any, is being further limited by the intended use recitation. Applicant's provision of a definition of conjugation is not found persuasive with regard to claim 148 because the definition does not clarify the interrelationships of the components of the composition.

Claims 134-137, 139-143, 148, and 150 are rejected under 35 U.S.C. 102(e) as being anticipated by Holder et al., US patent 5,720,859, filed Feb. 22, 1993, for reasons of record in the prior rejection of the similar subject matter of claims 68-116. This ground of rejection was inadvertently omitted from the previous Office action.

Holder et al., teach recombinant peptides derived from the 19kDa C-terminal fragment of the merozoite surface protein (MSP-1) of *P. falciparum* which comprise the 2 EGF regions of the p19 protein. The peptides are inherently characterized by the ability to induce long term memory immune responses and to inhibit parasitemia in *vivo*. The peptides are comprised in a vaccine administered with an appropriate adjuvant such as alum. Thus, the reference teachings anticipate the invention as instantly claimed.

Applicant's arguments filed 20 April 2001 and entered 20 June 2001 have been fully considered but they are not deemed to be persuasive. Notwithstanding applicant's arguments to the contrary, the reference clearly teaches vaccines comprising alum and recombinant conformational portions of the 19kDa C-terminal fragment of the merozoite surface protein (MSP-1) of *P. falciparum*.

Claims 153, 156, 159, 162, 165, 169, 172, and 175 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Longacre (Mol. Biochem. Parasitol. 74: 105-111, 1995) in view of Longacre et al. (Mol. Biochem. Parasitol. 64:191,

1994) for reasons of record in the prior rejection of the similar subject matter of claims 117-127, 129, 130, and 149.

Applicant's arguments filed 20 September 2002 have been fully considered but they are not deemed to be persuasive. Applicant urges that the combination of references do not teach recombinant proteins of the p19 fragment of *P. falciparum* MSP-1 protein. This is not found persuasive because the argument is of no moment with regard to the *P. cynomolgi* MSP-1 fragments as instantly claimed. Moreover, as set forth, Longacre teaches the cloning of the *P. cynomolgi* C-terminal MSP-1 protein sequence in the vector previously shown effective by Longacre et al. for the cloning of the C-terminal p42 and p19 fragments of the *P. vivax* MSP-1 protein in baculovirus. The argument is also not found persuasive because Longacre et al. admit that the construction of recombinant baculovirus expressing *P. vivax* MSP-1 protein fragments was guided by the previous functional constructs expressing the *P. falciparum* MSP-1 protein fragments.

Claims 151, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173, and 174 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chappel et al (Mol. Biochem. Parasitol. 60:303, 1993), Miller et al (Mol. Biochem. Parasitol. 59:1, 1993), Longacre et al (Mol. Biochem. Parasitol. 64:191, 1994), and Longacre (Mol. Biochem. Parasitol. 74: 105-111, 1995).

Chappel et al teach a recombinant baculovirus, similar in construction to that as instantly disclosed, i.e. having the amino terminal 34 amino acids of the *P. falciparum* MSP-1 protein fused to 271 amino acid residues of the p42 fragment of the protein ending at residue 1723 of the sequence as disclosed and numbered in Miller et al (see page 6), which produces a soluble protein (because it lacks the putative glycosylphosphatidylinositol addition region C-terminal to the second EGF-like domain) and which includes both EGF-like domain structures of the p19 fragment of the MSP-1 protein. The reference teaches that the first EGF-like domain of the p19 fragment, by itself, contains many of conformational epitopes recognized by known antibodies which bind to both the p42 and p19 fragments and inhibit parasite growth. In contrast to the invention as instantly claimed, the reference does not teach production of p19 fragments or the use of the N-terminal amino acids of the *Plasmodium vivax* MSP-1 protein.

Longacre et al. teach recombinant baculovirus constructs comprising nucleic acid sequences encoding N-terminal amino acids of the *Plasmodium vivax* MSP-1 protein, either anchored or secreted forms of both the C-terminal p42 fragment (which comprises the C-terminal p19 fragment) and the C-terminal p19 fragment of the *Plasmodium vivax* MSP-1 protein, and two TAA stop codons, all under the control of the polyhedrin promotor. The reference admits that the construction of recombinant baculovirus comprising *Plasmodium vivax* MSP-1 protein fragments was guided by the previous functional constructs expressing the *P. falciparum* MSP-1 protein fragments. Longacre et al. demonstrate that these baculovirus constructs containing an appropriate MSP-1 signal sequence

can be used for the expression of various length soluble or anchored C-terminal fragments of the MSP-1 protein.

Longacre teaches the cloning of the *Plasmodium cynomolgi* C-terminal MSP-1 protein sequence in the vector previously shown effective by Longacre et al (Mol. Biochem. Parasitol. 64:191, 1994) for the cloning of the C-terminal p42 and p19 fragments of the *P. vivax* MSP-1 protein in baculovirus, including the use of the nucleic acid sequences encoding N-terminal amino acid leader sequence of the *Plasmodium vivax* MSP-1 protein. The reference suggests the use of the fragments for vaccine studies.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have constructed a recombinant baculovirus expressing at least the first EGF-like domain of the C-terminal p19 fragment of the *P. falciparum* MSP-1 protein using any of the genus of nucleotide sequences encoding the relevant amino acid sequence (Chappel et al in view of Miller et al) with well known methods, as in Chappel et al and Longacre et al, with an extremely reasonable expectation of success that the encoded sequence would be expressed by insect cells containing the baculovirus constructs in view of the successful production of a variety of like soluble and/or anchored MSP-1 fragments as taught in Chappel et al or Longacre et al. The substitution of *P. vivax* signal and anchoring encoding sequences known to function for expression of the fragments of the protein in insect cells for the homologous sequences encoded by *P. falciparum* is well within the skill of an ordinary practitioner in the art and would not have been expected to influence the immunological function of

the *P. falciparum* encoded and expressed p19 fragment in view of the teachings of Chappel et al that the first EGF-like domain of the C-terminal p19 fragment of the *P. falciparum* MSP-1 protein, by itself, contains many of conformational epitopes recognized by known antibodies which bind to both the p42 and p19 fragments and inhibit parasite growth, and in view of the successful use of the *P. vivax* leader sequence in a plasmid encoding the C-terminal fragment of the MSP-1 protein of *Plasmodium cynomolgi*.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 134-137, 139-141, 143, 145, 148, 149, and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Longacre in view of Longacre et al. as applied to claims 153, 156, 159, 162, 165, 169, 172, and 175 above, and further in view of Holder et al. (U.S. Pat. No. 5,720,859).

Claims 134-137, 139-143, 148, and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappel et al., Miller et al., Longacre, and Longacre et al. as applied to claims 151, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173, and 174 above, and further in view of Holder et al. (U.S. Pat. No. 5,720,859).

The teachings of Chappel et al., Miller et al., Longacre, and Longacre et al. are as set forth previously and differ from the invention as instantly claimed in not teaching incorporation of recombinant MSP-1 peptides in vaccine compositions with alum.

The teachings of Holder et al. are as set forth above.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have incorporated the recombinant MSP-1 peptides taught by Longacre in view of Longacre et al. or Chappel et al., Miller et al., Longacre, and Longacre et al. in a vaccine composition comprising alum because the recombinant MSP-1 peptides are suggested for use in vaccines and Holder et al. teach the incorporation of MSP-1 peptides comprising the EGF domains in vaccine compositions comprising alum.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Applicant's arguments filed 20 September 2002 have been fully considered but they are not deemed to be persuasive in view of the NEW GROUNDS of rejection set forth herein.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any of Murphy et al (Parasitology 100: 177-183, 1990), Chang et al. (J. Immunology 149: 548-555, 1992), Blackman et al. (FEMS Immunology and Medical Microbiology 6: 307-316, 1993), Egan et al. (Infection & Immunity 63(2): 456-466, Feb. 1995), Chang et al. (Infection & Immun. 64(1): 253-261, Jan., 1996), Shi et al. (Infection and Immunity 64(7): 2716-2723, July 1996), or Egan et al. (Infection and Immunity 65(8): 3024-3031, August 1997) teach recombinant

proteins comprising the sequence of the p19 fragment of the *P. falciparum* MSP-1 protein capable of expressing native conformational epitopes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

James L. Grun, Ph.D.
August 23, 2004

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
8/27/04